

Synthesis of Methyl Diantilis

Laboratory adapted from: W.H. Miles, K.B. Connell "Synthesis of Methyl Diantilis, a Commercially Important Fragrance" *Journal of Chemical Education* **2006**, 83, 285.

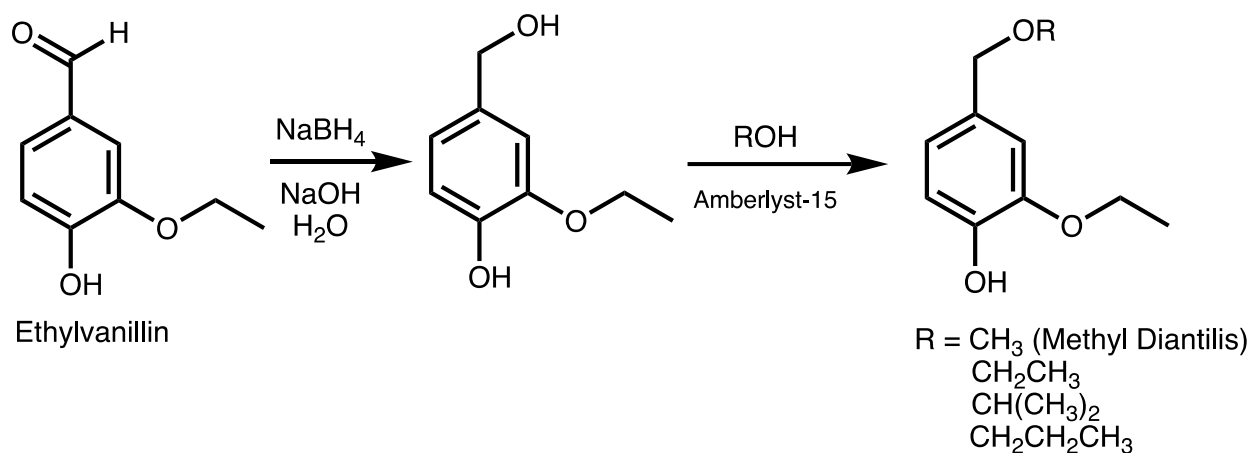
A person born three thousand years ago with a penchant for organic chemistry would have been a dyer or perfumer. The beginnings of both the dye industry and the fragrance industry (and the related flavor industry) are firmly rooted in organic chemistry. The dye industry was a world filled with brewing pots of herbs or even animals. Now synthetic dyes dominate the industry; only one natural dye (indigo) used before 1850 has any economic importance. Indigo was once prepared from the indigo plant (genus *Indigofera*), but it is now prepared in chemical factories. Although synthetic chemicals have made significant inroads into the fragrance industry, chemicals from natural products still constitute about fifty percent of the compounds used in the flavor and fragrance industry today.

The "olfactory spectrum" is one way of depicting the many distinct odor notes humans perceive. Perfumers characterize compounds (or mixture of compounds) as fruity, green, marine, floral, spicy, woody, ambery, or musky. The subtle combination of these different odor notes leads to the perfumes we pay such a high price for. The actual raw materials cost of many perfumes is often quite low, but we pay a premium for that special (and proprietary) combination of odorants.

The scientific understanding of the sense of smell is still in its infancy. Considerable research has been directed towards the identification of the receptors responsible for our perception of chemicals. The 2004 Nobel Prize was awarded to Richard Axel of Howard Hughes Medical Institute at Columbia University and Linda Buck of the Fred Hutchinson Cancer Research Center in Seattle for their pioneering work in identifying a large gene family that produces over a thousand different types of olfactory receptors. Even if we had a complete scientific understanding of the biochemistry of smell, the sense of smell would transcend science. Smelling elicits intense emotions, which is not surprising since the olfactory bulb is connected to the limbic system, a very primitive part of our brains. In this experiment you will prepare a class of compounds whose smell will be very familiar to you. The ethanolic extracts of the orchid *Vanilla planifolia* gives a flavoring agent often used in baking: vanilla. There are many different compounds in vanilla extract, but the primary one responsible for the olfactory sensation is vanillin (4-hydroxy-3-methoxybenzaldehyde), a phenol. Vanillin and vanilla extract, as well as related compounds such as isoeugenol (2-methoxy-4-propenylphenol), are used in many fragrances. Fragrance chemists continue to search for compounds that have this odor note but also have other odor notes or better physical and chemical properties. Our experiment will be based on the research of Givaudan, a major flavor and fragrance company. They described in a patent the synthesis of a family of odorants related to vanillin. One of the compounds described in the patent, 4-hydroxy-3-ethoxybenzyl methyl ether, was recently "launched" under the trade name Methyl Diantilis. This compound, which has a "spicy, carnation, sweet, vanilla" olfactive note, resembles isoeugenol, an important commercial fragrance. Methyl Diantilis (named after carnations, *Dianthus caryophyllus*), however, does not discolor as readily as isoeugenol, an important attribute in perfume compositions.

Synthetic Scheme:

Some of you will synthesize Methyl Diantilis, but others will synthesize related 4-hydroxy-3-ethoxybenzyl alkyl ethers, which were also described in the patent for Methyl Diantilis. You will use the synthetic scheme described by the Givaudan chemists in their patent with some modifications. You will reduce the aldehyde with sodium borohydride. In industry on a large scale, this reduction would be done with hydrogen, the most inexpensive reducing agent. The etherification process using NaHSO_4 , as described in the patent, is not as clean as with "wet" Amberlyst® 15, a very strong polymeric acid. The use of an insoluble polymer for this reaction reflects one of the major trends in organic synthesis. Although polymer supported reagents have been used in peptide synthesis since the 1960's (the Merrifield synthesis), the use of these reagents for the synthesis of more typical organic compounds did not become widespread until the explosive growth of combinatorial chemistry. The work-up procedure, filtering the insoluble polymer from the soluble product, is very simple.



Background Reading:

- 1) Pedersen text, Ch. 7.2.2 (pipette filtration)
- 2) Karty text, Ch. 17.3 (NaBH_4 reduction of ketones).

Pre-Lab:

Prepare your lab notebook. **For your Table of Chemicals, write down names, structures, molecular weights, amount to be used (g or mL), amount to be used (mol) and densities (for liquids) for ethylvanillin, NaBH_4 , methanol, ethanol, 1-propanol, and 2-propanol. Also include the amount of Amberlyst to be used in g.** Write up any safety notes for these materials and the procedure. Write down a step-by-step procedure that allows you to complete the experiment based on your notebook without reference to this procedure document. In addition, complete the questions marked "Pre-Lab" on your lab worksheet.

Procedure:

Overview of Group Work

- Divide into groups of 4.
- Each student will do Step 1. One student's product from step 1 will be chosen for ^1H NMR analysis. (so there will be one ^1H NMR spectrum per group of 4).
- Each student will use the product from Step 1 to make an ether with one of four alcohols. Each group of 4 will therefore synthesize each product derivative.
- ^1H NMR will be taken of each of the four product ethers.
- All students will use all spectra from the group to write their formal report.

Step 1: Sodium Borohydride Reduction of 3-Ethoxy-4-hydroxybenzaldehyde (Ethylvanillin)

- Dissolve 0.243 g of 3-ethoxy-4-hydroxybenzaldehyde in 3.0 mL of 0.5 M NaOH in a 25mL Erlenmeyer flask with a magnetic stir bar.
- Cool the flask in an ice bath and add in small amounts 0.075 g of NaBH_4 .
- Remove flask from the ice bath and allow it to come to room temperature over 20 minutes
- Cool the reaction flask again by placing it in an ice bath, then slowly add 2.5M HCl.
- CAUTION: Add the HCl slowly, as there will be a lot of foaming! Hydrogen gas is formed!
- Check the acidity of the reaction once the gas formation decreases (after ~ 1 mL).
- Keep adding HCl until the reaction has become acidic.
- Let the flask sit in the ice bath for an additional 5 minutes.
- Vacuum filter the precipitate, washing with cold water three times (3 x 2mL).
- Allow the solid to dry on the filter paper under vacuum for 15+ minutes.
- Weigh product and record its mass/appearance in your notebook.
- Run TLC of product compared to ethyl vanillin.
- Choose one student in the group's product to prepare an NMR sample in DMSO- d_6 .

Step 2: Etherification of 3-ethoxy-4-hydroxybenzyl Alcohol

- Transfer 0.1 g of 'wet' Amberlyst into a small round bottom flask.
- Wash the Amberlyst three times with 1 mL portions of your alcohol (methanol, ethanol, 1-propanol, or 2-propanol).
- Carefully remove the alcohol from the resin with a Pasteur pipette.
- Add 2 mL of your alcohol to the alcohol-rinsed Amberlyst, then with vigorous stirring add 0.10 g of 3-ethoxy-4-hydroxybenzyl alcohol (product from Step 1) in small portions.
- Remove one drop of the reaction for TLC analysis.
- Place a condenser on the reaction flask and heat to reflux for 15 minutes.
- Lift the reaction flask out of the sand bath, remove one drop of the reaction and dilute the drop with 5 drops of acetone; check by TLC.
- If there is not complete conversion, heat the reaction to reflux for another 15 minutes.
- Add 0.050g of NaHCO_3 and stir for 5 more minutes.
- Filter by Pasteur pipette with a glass fiber plug, washing the reaction flask with small portions of your alcohol.
- Gently remove the solvent on a hot plate with a gentle stream of air. DO NOT OVERHEAT.
- Weigh product and record its mass/appearance in your notebook.
- Prepare NMR sample in DMSO- d_6 .